

**REMARKS**

The Examiner has required election one of the following groups for prosecution in this application:

**Group I:** Claims 11-15 and 17, drawn to an adenovirus vector comprising a promoter operably linked to a P972 gene.

**Group II:** Claims 19-20, drawn to a method of treating cancer in a mammal using an adenovirus vector comprising a promoter operably linked to a P972 gene.

In response, Applicants elect the claims of **Group II, claims 19-20**, without traverse.

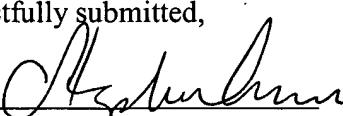
In addition, new claims 21-37 have been added. Support for these new claims can be found in the specification at page 9, line 8, to page 10, line 7; Figures 4-6; and Examples 6 and 7 on page 14 and 15. Support for the claims to "metastatic" is found in the three attached abstracts by Yu et al., Spiryda et al., and Bresalier et al., which demonstrate that MCF-7, He-La, and HM-7 colon cancer cells used in the experiments are metastatic. Support for the claims to "estrogen receptor" expressing tumor cells is found in the fourth attached abstract by Welshons et al.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: September 13, 2004

Respectfully submitted,

By

  
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Inhibition of Breast Cancer Metastasis by Heregulin-Beta 1

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**Authors:** Yu, Dihua; TEXAS UNIV AT HOUSTON

**Abstract:** The major goal of this Idea proposal is to determine whether and how HRG-Beta1 inhibits breast cancer metastasis and to identify the functional domains that are sufficient for inhibition of breast cancer metastasis. We have fulfilled most of the proposed tasks for the first year of the grant support. We demonstrated that the recombinant HRG-Beta1 can transcriptionally upregulate gelatinases activity. We found that HRG-Beta1 induces the aggregation (a metastasis associated property) of breast cancer cells via activation of PI-3-K but independent of ERK (Cancer Res. 59:1620-1625, 1999). To determine the effect of HRG- f3 1 in metastasis in vivo, we subcloned the extracellular domain of the full length HRG-Beta1 into the pSecTag2 expression vector, transfected it into MDA-MB-435 and MCF-7 cell, and established stable transfecants. To further delineate the domain(s) of HRG-Beta1 that regulates invasion/metastasis of breast cancer cells, we have also cloned the egf-like domain of HRG-Beta1 to pSecTag2 expression vector. We are transfecting the egf-like domain of HRG-Beta1 into MDA-MB-435 and MCF-7 cells to establish stable transfecants. These initial works have paved a productive avenue for the next grant-support year, when we will gain more insights regarding the role of HRG-Beta1 in breast cancer metastasis.

**Limitations:** APPROVED FOR PUBLIC RELEASE

**Description:** Annual rept. 1 Jun 1998-31 May 1999

**Pages:** 38

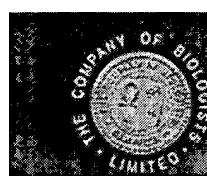
**Report Date:** JUN 1999

**Report number:** A180483

**Price:** \$21.95 (26% savings) - Shipping terms

**KEYWORDS RELATING TO THIS REPORT**

- BREAST CANCER
- LIGANDS
- METASTASIS
- MUTATIONS
- GENES
- CHEMORECEPTORS
- TRANSFECTION
- INHIBITION
- GROWTH SUBSTANCES
- ANTINEOPLASTIC AGENTS



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## JOURNAL ARTICLES

# Suppression of tumorigenicity in an aggressive cervical carcinoma induced by protein zero, a nervous system IgCAM

LB Spiryda and DR Colman

Department of Cell Biology and Brookdale Center for Developmental and Molecular Biology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA. [spiryda@msvax.mssm.edu](mailto:spiryda@msvax.mssm.edu)

In mammals, protein zero (P0), a neural IgCAM, is expressed solely in the peripheral nervous system where it mediates self-adhesion of Schwann cell membranes as compact myelin is generated. We show that when P0 is expressed in HeLa, a cervical carcinoma cell line, cells regain adhesion-mediated growth control, including the acquisition of contact inhibition and loss of anchorage-independent growth. Additionally, P0-expressing HeLa cells lose the ability to invade an artificial matrix, which correlates with decreased secretion of matrix-degrading enzymes. Lastly, and of great interest, unlike the aggressively metastatic cell line from which they were derived, P0-HeLa cells are neither tumorigenic nor metastatic when injected into athymic nude mice. By all these criteria, P0 expression appears to efficiently suppress in the long term, the transformed state of this carcinoma cell line. N-cadherin and its intracellular partners plakoglobin, alpha- and beta-catenin were significantly upregulated in the P0-HeLa cells. It appears therefore that P0 induces epithelialization and suppression of tumorigenicity in HeLa through the activation of the cadherin/catenin signaling systems. We conclude that the forced expression of bona fide adhesion molecules, such as P0, may serve as 'upstream' inducers of an essentially dormant but undamaged adhesion program in carcinoma cells that ultimately triggers the re-acquisition of normal epithelial characteristics, thereby suppressing tumorigenicity. Therapeutically, it may be that intercellular adhesion, no matter how it is induced, may serve as a single master event that is able to induce reversion of the carcinomatous state.

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1: *Gastroenterology*. 1998 Aug;115(2):287-96.

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**Gastroenterology**

**Metastasis of human colon cancer is altered by modifying expression of the beta-galactoside-binding protein galectin 3.**

**Bresalier RS, Mazurek N, Sternberg LR, Byrd JC, Yunker CK, Nangia-Makker P, Raz A.**

Department of Medicine, Henry Ford Health Sciences Center, Detroit, Michigan USA.

**BACKGROUND & AIMS:** Galectin 3 is a beta-galactoside-binding protein whose expression has been correlated with advanced tumor stage in the colon, but direct evidence for a role in metastasis is lacking. The current study was designed to more directly establish the role of galectin 3 in colon cancer metastasis.

**METHODS:** Galectin 3 levels were manipulated in human colon cancer cells using eukaryotic expression constructs designed to express the complete galectin 3 complementary DNA in either the sense or antisense orientation. Liver colonization was assessed in athymic mice after splenic-portal inoculation or spontaneous metastasis during cecal growth. **RESULTS:** Introduction of galectin 3 antisense into metastatic colon cancer cells (LSLiM6, HM7) resulted in a significant reduction in galectin 3-specific messenger RNA and total and cell surface galectin 3 protein. Conversely, stable integration of galectin 3 in the sense orientation resulted in an increase in cellular and cell surface galectin 3 in cells with low metastatic potential (LS174T). Reduction in galectin 3 levels was associated with a marked decrease in liver colonization and spontaneous metastasis by LSLiM6 and HM7 cells, whereas up-regulation of galectin 3 resulted in increased metastasis by LS174T cells. **CONCLUSIONS:** This study provides direct evidence that galectin 3 plays an important role in colon cancer metastasis.

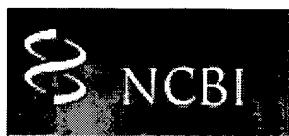
PMID: 9679034 [PubMed - indexed for MEDLINE]

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1: Mol Cell Endocrinol. 1993 Aug;94(2):183-94.

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## Subcellular compartmentalization of MCF-7 estrogen receptor synthesis and degradation.

Welshons WV, Grady LH, Judy BM, Jordan VC, Preziosi DE.

Department of Veterinary Biomedical Sciences, University of Missouri-Columbia 65211.

Turnover of the estrogen receptor protein was studied by using enucleation of human breast cancer-derived MCF-7 cells, to examine receptor synthesis and receptor degradation in the separated cytoplasmic compartment (cytoplasts) and nuclear compartment (nucleoplasts). Cytoplasts synthesized estrogen receptors measured by both hormone-binding and immunoassay, while estrogen receptors (but not progesterone or glucocorticoid receptors) were rapidly degraded in nucleoplasts with a half-life of 3-4 h. Little or no degradation of estrogen receptors in cytoplasts was observed under several conditions. Interestingly, MCF-7 cytoplasts contained approximately 15% of the cell's estrogen receptors, which were not 'translocated' by treatment with 17 beta-estradiol before enucleation. These results conclude that the estrogen receptor can be synthesized at least to a hormone binding form in the cytoplasm alone without requiring processing in the nucleus while the nucleus (or perinuclear cytoplasm) is the primary site of degradation of the estrogen receptor protein. In addition, the presence of a population of estrogen receptors that is cytoplasmic but nontranslocatable may need to be considered in the subcellular localization and actions of steroid receptors.

### MeSH Terms:

- Brain Neoplasms/chemistry\*
- Brain Neoplasms/metabolism\*
- Brain Neoplasms/ultrastructure
- Cell Nucleus/chemistry
- Cell Nucleus/metabolism
- Cell Nucleus/ultrastructure
- Cytoplasm/chemistry
- Cytoplasm/metabolism
- Cytoplasm/ultrastructure
- Estradiol/pharmacology
- Half-Life
- Human
- Immunoassay

- Leucine/metabolism
- Receptors, Estrogen/analysis\*
- Receptors, Estrogen/metabolism\*
- Receptors, Glucocorticoid/analysis
- Receptors, Glucocorticoid/metabolism
- Receptors, Progesterone/analysis
- Receptors, Progesterone/metabolism
- Subcellular Fractions/ultrastructure
- Support, Non-U.S. Gov't
- Support, U.S. Gov't, P.H.S.
- Tumor Cells, Cultured

**Substances:**

- Receptors, Estrogen
- Receptors, Glucocorticoid
- Receptors, Progesterone
- Estradiol
- Leucine

**Grant Support:**

- CA50354/CA/NCI

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